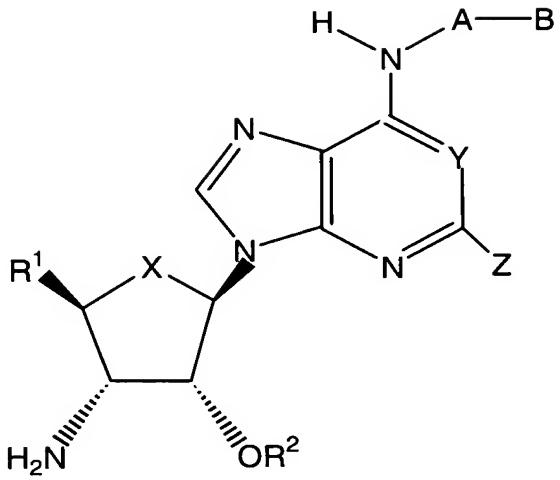
CLAIMS

What is claimed is:

1. A compound having Formula (I)



(I)

wherein

X is oxy, methylene or thio;

Y is CH or N;

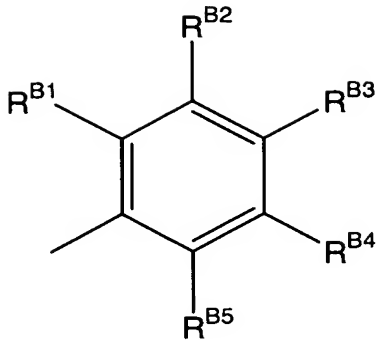
Z is H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkyloxy, trifluoromethyl or halo;

R^1 is hydroxymethyl, $(C_1\text{-}C_3)$alkoxymethyl, $(C_3\text{-}C_5)$cycloalkoxymethyl, carboxy, $(C_1\text{-}C_3)$alkoxycarbonyl, $(C_3\text{-}C_5)$cycloalkoxycarbonyl, 1,1-aminoiminomethyl, 1,1-(mono-N- or di-N,N-$(C_1\text{-}C_4)$alkylamino)iminomethyl, 1,1-(mono-N- or di-N,N-$(C_3\text{-}C_5)$cycloalkylamino)iminomethyl, carbamoyl, mono-N- or di-N,N-$(C_1\text{-}C_4)$alkylaminocarbonyl, mono-N- or di-N,N-$(C_3\text{-}C_5)$cycloalkyl-aminocarbonyl, or N-$(C_1\text{-}C_4)$alkyl-N-$(C_3\text{-}C_5)$cycloalkylaminocarbonyl;

R^2 is H, $(C_1\text{-}C_3)$alkyl or $(C_3\text{-}C_5)$cycloalkyl;

A is $-(CH_2)_n-$ where n is and integer from 1 to 4, or $-(C_mH_{2m-2})-$ where m is an integer from 3 to 6; and

B is hydrogen, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl, $-CH(aryl)_2$, or



where R^{B1}, R^{B2}, R^{B3}, R^{B4} and R^{B5} are each independently selected from the group consisting of hydrogen, $(C_1\text{-}C_4)$alkyl, halo, hydroxy, thio, amino, $(C_1\text{-}C_6)$alkyloxy, $(C_1\text{-}C_6)$alkylthio, $(C_1\text{-}C_6)$alkylamino and –D-G, where

D is oxy, thio, NH, $(C_1\text{-}C_6)$alkyloxy, $(C_1\text{-}C_6)$alkylthio or $(C_1\text{-}C_6)$alkylamino and

G is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, wherein G is optionally mono-, di- or tri-substituted independently with halo, $(C_1\text{-}C_3)$alkyl, trifluoromethyl, trifluoromethoxy, nitro, cyano, $(C_3\text{-}C_5)$cycloalkyl, hydroxy or $(C_1\text{-}C_3)$alkoxy, or

G is cyano, $(C_1\text{-}C_4)$alkoxycarbonyl, $(C_3\text{-}C_5)$cycloalkoxycarbonyl, $C(O)NR^4R^5$, $C(S)NR^4R^5$, $C(NH)NR^4R^5$, $C(N(C_1\text{-}C_3)\text{alkyl})NR^4R^5$ or $C(N(C_3\text{-}C_{10})\text{cycloalkyl})NR^4R^5$, where

R^4 is H, $(C_1\text{-}C_{10})$alkyl, hydroxy, $(C_1\text{-}C_{10})$alkoxy, $(C_3\text{-}C_{10})$cycloalkoxy or a partially saturated, fully saturated or fully unsaturated five to eight membered ring, optionally linked through $(C_1\text{-}C_3)$alkyl, optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen, or, a bicyclic ring or a bicyclic ring with optional $(C_1\text{-}C_3)$ bridge optionally linked through $(C_1\text{-}C_3)$alkyl, said bicyclic ring or bridged bicyclic ring optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen wherein said $(C_1\text{-}C_{10})$alkyl, $(C_1\text{-}C_{10})$alkoxy, $(C_3\text{-}C_{10})$cycloalkoxy or R^4 ring(s) is optionally mono-, di- or tri-substituted independently with halo, $(C_1\text{-}C_3)$alkyl, trifluoromethyl, nitro, cyano, $(C_3\text{-}C_5)$cycloalkyl, hydroxy or $(C_1\text{-}C_3)$alkoxy, and

R^5 is H, $(C_1\text{-}C_{10})$alkyl or $(C_1\text{-}C_{10})$cycloalkyl; or R^4 and R^5 taken together with the nitrogen to which they are attached form a fully saturated or partially

unsaturated four to nine membered ring, said ring optionally bridged, optionally having one to three additional heteroatoms selected independently from oxygen, sulfur and nitrogen, said ring optionally mono- or di-substituted independently with oxo, hydroxy, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_8)$alkyl, amino, mono-N- or di-N,N-$(C_1$-$C_4)$alkylaminocarbonyl, mono-N- or di-N,N-$(C_3$-$C_5)$cycloalkyl- aminocarbonyl, N-$(C_1$-$C_4)$alkyl-N-$(C_3$-$C_5)$cycloalkylaminocarbonyl, mono-N- or di-N,N-$(C_1$-$C_4)$alkylamino, mono-N- or di-N,N-$(C_3$-$C_5)$cycloalkylamino, N-$(C_1$-$C_4)$alkyl-N-$(C_3$-$C_5)$cycloalkylamino, formylamino, $(C_1$-$C_4)$alkylcarbonylamino, $(C_3$-$C_5)$cycloalkylcarbonylamino, $(C_1$-$C_4)$alkoxycarbonylamino, N-$(C_1$-$C_4)$alkoxycarbonyl-N-$(C_1$-$C_4)$alkylamino, $(C_1$-$C_4)$sulfamoyl, $(C_1$-$C_4)$alkylsulfonylamino, $(C_3$-$C_5)$cycloalkylsulfonylamino or a partially saturated, fully saturated or fully unsaturated five to eight membered ring, optionally linked through $(C_1$-$C_3)$alkyl, optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally linked through $(C_1$-$C_3)$alkyl, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, optionally mono- or di-substituted with halo, trifluoromethyl, trifluoromethoxy, $(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$alkoxy;

provided that A is not $-(CH_2)_1-$, when R^{B1} is –D-G, R^{B4} is halo, trifluoromethyl, cyano, $(C_1$-$C_3)$ alkyl, $(C_1$-$C_3)$ alkyloxy, ethenyl or ethynyl, and R^{B2}, R^{B3} and R^{B5} are hydrogen;

a prodrug thereof, or a pharmaceutically acceptable salt, hydrate or solvate of said compound or said prodrug.

2. The compound of Claim 1 wherein

X is oxy;

Y is N;

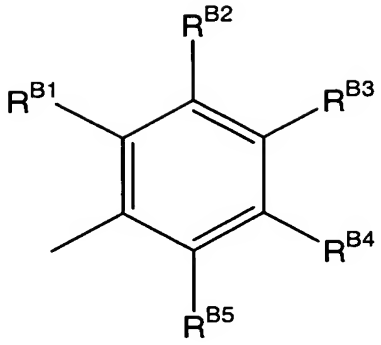
Z is H or Cl;

R^1 is $(C_1$-$C_6)$alkylcarbamoyl;

R^2 is H;

A is $-(CH_2)_n-$, where n is 1 or 2, or cyclopropyl; and

B is substituted or unsubstituted heteroaryl, naphthyl, $-CH(aryl)_2$, or



where R^{B1}, R^{B2}, R^{B3}, R^{B4} and R^{B5} are each independently selected from the group consisting of hydrogen, $(C_1\text{-}C_4)$alkyl, halo, hydroxy, thio, amino, $(C_1\text{-}C_6)$alkyloxy, $(C_1\text{-}C_6)$alkylthio, $(C_1\text{-}C_6)$alkylamino and –D-G, where

D is oxy, thio, $(C_1\text{-}C_6)$alkyloxy or $(C_1\text{-}C_6)$alkylthio, and

G is phenyl, pyridyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, isoxazolyl, pyridinazinyl, tetrazolyl, isothiazolyl, thiophenyl, furanyl, 1,2,4-oxadiazolyl, 1,2,4-thiadiazolyl, pyrazolyl, pyrrolyl, indolyl, naphthalenyl, quinolinyl, isoquinolinyl, benzo[b]furanyl, benzo[b]thiophenyl, benzothiazolyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, tetrahydropyranyl, morpholinyl wherein said G is optionally mono-, di- or tri-substituted independently with halo, $(C_1\text{-}C_3)$alkyl or $(C_1\text{-}C_3)$alkoxy;

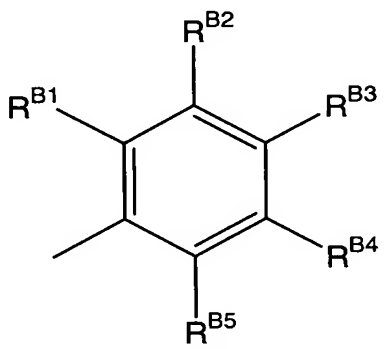
a prodrug thereof, or a pharmaceutically acceptable salt, hydrate or solvate of said compound or said prodrug.

3. The compound of Claim 2 wherein B is a substituted or unsubstituted pyridyl, indolyl or thiazolyl; a prodrug thereof, or a pharmaceutically acceptable salt, solvate, or hydrate of said compound or said prodrug.

4. The compound of Claim 3 wherein said substituted pyridyl, indolyl or thiazolyl is substituted with at least one substituent selected from the group consisting of $(C_1\text{-}C_4)$alkyl, halo, hydroxy, thio, amino, $(C_1\text{-}C_6)$alkyloxy, $(C_1\text{-}C_6)$alkylthio, $(C_1\text{-}C_6)$alkylamino and –D-G, where D is oxy, thio, $(C_1\text{-}C_6)$alkyloxy or $(C_1\text{-}C_6)$alkylthio, and G is phenyl, pyridyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, isoxazolyl, pyridinazinyl, tetrazolyl, isothiazolyl, thiophenyl, furanyl, 1,2,4-oxadiazolyl, 1,2,4-thiadiazolyl, pyrazolyl, pyrrolyl, indolyl, naphthalenyl, quinolinyl, isoquinolinyl, benzo[b]furanyl, benzo[b]thiophenyl, benzothiazolyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, tetrahydropyranyl, morpholinyl wherein said G is optionally mono-, di- or tri-substituted independently with halo, $(C_1\text{-}C_3)$alkyl or $(C_1\text{-}C_3)$alkoxy; a

prodrug thereof, or a pharmaceutically acceptable salt, solvate, or hydrate of said compound or said prodrug.

5. The compound of Claim 2 wherein B is



where R^{B1}, R^{B2}, R^{B3}, R^{B4} and R^{B5} are each independently selected from the group consisting of hydrogen, $(C_1\text{-}C_4)$alkyl, halo, hydroxy, $(C_1\text{-}C_6)$alkyloxy and –D-G, where

D is $(C_1\text{-}C_6)$alkoxy and

G is phenyl, pyridyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, furanyl, 1,2,4-oxadiazolyl, 1,2,4-thiadiazolyl, pyrazolyl, pyrrolyl, or morpholinyl wherein said G is optionally mono-, di- or tri-substituted independently with halo, $(C_1\text{-}C_3)$alkyl, trifluoromethoxy or $(C_1\text{-}C_3)$alkoxy;

a prodrug thereof, or a pharmaceutically acceptable salt, hydrate or solvate of said compound or said prodrug.

6. A compound selected from the group consisting of

(2S,3S,4R,5R) 3-amino-5-{6-[2-(2,5-dimethoxy-phenyl)-ethylamino]-purin-9-yl}-4-hydroxy-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-4-hydroxy-5-[6-(3-methoxy-benzylamino)-purin-9-yl]-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-5-[6-(4-benzyloxy-benzylamino)-purin-9-yl]-4-hydroxy-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-4-hydroxy-5-[6-(2-hydroxy-5-methoxy-benzylamino)-purin-9-yl]-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-5-[6-(3-butoxy-benzylamino)-purin-9-yl]-4-hydroxy-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-5-[6-(2,5-dimethyl-benzylamino)-purin-9-yl]-4-hydroxy-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-5-[6-(2,5-dichloro-benzylamino)-purin-9-yl]-4-hydroxy-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-4-hydroxy-5-{6-[3-(2-morpholin-4-yl-ethoxy)-benzylamino]-purin-9-yl}-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-4-hydroxy-5-{6-[3-(3-methyl-isoxazol-5-ylmethoxy)-benzylamino]-purin-9-yl}-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-4-hydroxy-5-[6-(2-methoxy-5-methyl-benzylamino)-purin-9-yl-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-5-[6-(2,5-diethyl-benzylamino)-purin-9-yl]-4-hydroxy-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-5-{6-[2-(1-ethyl-propoxy)-5-methoxy-benzylamino]-purin-9-yl}-4-hydroxy-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-5-[6-(3-cyclopentyloxy-benzylamino)-purin-9-yl]-4-hydroxy-tetrahydro-furan-2-carboxylic acid methylamide.

(2S,3S,4R,5R) 3-amino-5-[6-(2-cyclopentyloxy-benzylamino)-purin-9-yl]-4-hydroxy-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-5-[6-(5-chloro-2-isopropoxy-benzylamino)-purin-9-yl]-4-hydroxy-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-5-[6-(2-benzyloxy-benzylamino)-purin-9-yl]-4-hydroxy-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-5-{6-[2-(4-fluoro-phenyl)-ethylamino]-purin-9-yl}-4-hydroxy-tetrahydro-furan-2-carboxylic acid methylamide.

(2S,3S,4R,5R) 3-amino-5-{6-[2-(4-benzyloxy-3,5-dimethoxy-phenyl)-ethylamino]-purin-9-yl}-4-hydroxy-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-4-hydroxy-5-(6-methylamino-purin-9-yl)-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-5-{6-[2-(4-fluoro-3-methoxy-phenyl)-ethylamino]-purin-9-yl}-4-hydroxy-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-5-{6-[(3-benzyloxy-6-methyl-pyridin-2-ylmethyl)-amino]-purin-9-yl}-4-hydroxy-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-5-[6-(2,2-diphenyl-ethylamino)-purin-9-yl]-4-hydroxy-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-5-[2-chloro-6-(2,5-dimethoxy-benzylamino)-purin-9-yl]-4-hydroxy-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-5-{6-[2-(3-benzyloxy-4-methoxy-phenyl)-ethylamino]-purin-9-yl}-4-hydroxy-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-4-hydroxy-5-[6-(2-pyridin-3-yl-ethylamino)-purin-9-yl]-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-5-[6-(2,5-dimethoxy-benzylamino)-purin-9-yl]-4-hydroxy-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-4-hydroxy-5-(6-phenethylamino-purin-9-yl)-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-5-(2-chloro-6-methylamino-purin-9-yl)-4-hydroxy-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-4-hydroxy-5-[6-(2-phenyl-cyclopropylamino)-purin-9-yl]-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-5-[2-chloro-6-(2,5-dichloro-benzylamino)-purin-9-yl]-4-hydroxy-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-4-hydroxy-5-{6-[2-(2-morpholin-4-yl-thiazol-5-yl)-ethylamino]-purin-9-yl}-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-4-hydroxy-5-[6-(2-naphthalen-1-yl-ethylamino)-purin-9-yl]-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-5-{6-[(5-fluoro-1H-indol-3-ylmethyl)-amino]-purin-9-yl}-4-hydroxy-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-5-{6-[2-(4-benzyloxy-3-methoxy-phenyl)-ethylamino]-purin-9-yl}-4-hydroxy-tetrahydro-furan-2-carboxylic acid methylamide,

(2S,3S,4R,5R) 3-amino-4-hydroxy-5-[6-(2-pyridin-2-yl-ethylamino)-purin-9-yl]-tetrahydro-furan-2-carboxylic acid methylamide, and

(2S,3S,4R,5R) 3-amino-4-hydroxy-5-[6-(2-phenyl-cyclopropylamino)-purin-9-yl]-tetrahydro-furan-2-carboxylic acid methylamide;

a prodrug thereof, or a pharmaceutically acceptable salt, solvate, or hydrate of said compound or said prodrug.

7. A method of reducing tissue damage resulting from ischemia or hypoxia comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound, a prodrug thereof, or

pharmaceutically acceptable salt, solvate, or hydrate of said compound or said prodrug according to Claim 1.

8. The method of Claim 7 wherein the tissue is cardiac, brain, liver, kidney, lung, gut, skeletal muscle, spleen, pancreas, nerve, spinal cord, retina tissue, the vasculature, or intestinal tissue.

9. The method of Claim 7 wherein said effective amount of said compound, prodrug thereof, or pharmaceutically acceptable salt, hydrate or solvate of said compound or said prodrug is about 0.01 mg/kg/day to about 50 mg/kg/day.

10. The method of Claim 9 wherein said mammal is a human.

11. The method of Claim 10 wherein the compound is administered prior to, during and after cardiac surgery.

12. A pharmaceutical composition which comprises a therapeutically effective amount of a compound, a prodrug thereof, or pharmaceutically acceptable salt, solvate, or hydrate of said compound or said prodrug according to Claim 1, and a pharmaceutically acceptable carrier, vehicle or diluent.

13. A pharmaceutical kit comprising

a) a dosage form adapted for intravenous or intramuscular injection comprising a compound, a prodrug thereof, or pharmaceutically acceptable salt, solvate, or hydrate of said compound or said prodrug according to Claim 1; and

b) instructions describing a method of using the dosage form to reduce tissue damage resulting from ischemia or hypoxia.

14. A pharmaceutical combination composition comprising: a therapeutically effective amount of a composition comprising

a) a first compound, said first compound being a compound, a prodrug thereof, or pharmaceutically acceptable salt, solvate, or hydrate of said compound or said prodrug according to Claim 1;

b) a second compound, said second compound being a cardiovascular agent, a glycogen phosphorylase inhibitor, a sorbitol dehydrogenase inhibitor, or an aldose reductase inhibitor; and

c) a pharmaceutical carrier, vehicle or diluent.

15. The pharmaceutical composition of Claim 14 wherein the aldose reductase inhibitor is 1-phthalazineacetic acid, 3,4-dihydro-4-oxo-3-[[5-trifluoromethyl)-2-benzothiazolyl]methyl]-, or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

16. The pharmaceutical composition of Claim 14 wherein the glycogen phosphorylase inhibitor is

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-((3S)-hydroxypyrrolidin-1-yl)-3-oxopropyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl -3-((3S,4S)-dihydroxypyrrolidin-1-yl) -(2R)-hydroxy- 3-oxopropyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [(1S)- ((R)-hydroxy-dimethylcarbamoyl-methyl)-2-phenyl-ethyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [(1S)- ((R)-hydroxy-methoxy-methyl-carbamoyl)-methyl)-2-phenyl-ethyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [(1S)- ((R)-hydroxy-[(2-hydroxy-ethyl)-methyl-carbamoyl]-methyl)-2-phenyl-ethyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(3-hydroxyimino-pyrrolidin-1-yl)-2-oxo-ethyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl -3-((cis)-dihydroxypyrrolidin-1-yl) -(2R)-hydroxy- 3-oxopropyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [2-(1,1-dioxo-thiazolidin-3-yl)-2-oxo-ethyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [(1S)-(4-fluoro-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3RS)-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [2-oxo-2-((1RS)-oxo-thiazolidin-3-yl)-ethyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-amide;

or a pharmaceutically acceptable salt, hydrate or solvate thereof.

17. The pharmaceutical composition of Claim 14 wherein the cardiovascular agent is a β-blocker, a calcium channel blocker, a potassium channel opener, adenosine, adenosine receptor agonists, an ACE inhibitor, a nitric oxide donor, a diuretic, a glycoside, a thrombolytic, a platelet inhibitor, aspirin, dipyridamol, potassium chloride, clonidine, prazosin, pyruvate dehydrogenase kinase inhibitors, pyruvate dehydrogenase complex activators, biguanides, NHE-1 inhibitor, angiotensin II receptor antagonists, C5a inhibitors, soluble complement receptor type 1 or analogues thereof, partial fatty acid oxidation inhibitors, acetyl CoA carboxylase activators, malonyl CoA decarboxylase inhibitors, 5'AMP-activated protein kinase inhibitors, adenosine nucleoside inhibitors, anti-apoptotic agents, monophosphoryl lipid A or analogues, nitric oxide synthase activators/inhibitors, protein kinase C activators, protein kinase δ inhibitors, poly (ADP ribose) synthetase inhibitors, metformin, endothelin coverting enzyme inhibitors, endothelin ET A receptor antagonists, TAFI inhibitors, or a Na/Ca exchanger modulators.

18. The pharmaceutical composition of Claim 17 wherein the NHE-1 inhibitor is

[1-(8-bromoquinolin-5-yl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(6-chloroquinolin-5-yl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(indazol-7-yl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(benzimidazol-5-yl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(1-isoquinolyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine;

[5-cyclopropyl-1-(4-quinolinyl)-1*H*-pyrazole-4-carbonyl]guanidine;

[5-cyclopropyl-1-(quinolin-5-yl)-1H-pyrazole-4-carbonyl]guanidine;

[5-cyclopropyl-1-(quinolin-8-yl)-1H-pyrazole-4-carbonyl]guanidine;

[1-(indazol-6-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(indazol-5-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(benzimidazol-5-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(1-methylbenzimidazol-6-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(5-quinolinyl)-5-*n*-propyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(5-quinolinyl)-5-isopropyl-1*H*-pyrazole-4-carbonyl]guanidine;

[5-ethyl-1-(6-quinolinyl)-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(2-methylbenzimidazol-5-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(1,4-benzodioxan-6-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(benzotriazol-5-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(3-chloroindazol-5-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(5-quinolinyl)-5-butyl-1*H*-pyrazole-4-carbonyl]guanidine;

[5-propyl-1-(6-quinolinyl)-1*H*-pyrazole-4-carbonyl]guanidine;

[5-isopropyl-1-(6-quinolinyl)-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(2-chloro-4-methylsulfonylphenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(2-chlorophenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(2-trifluoromethyl-4-fluorophenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(2-bromophenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(2-fluorophenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(2-chloro-5-methoxyphenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(2-chloro-4-methylaminosulfonylphenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(2,5-dichlorophenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(2,3-dichlorophenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(2-chloro-5-aminocarbonylphenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(2-chloro-5-aminosulfonylphenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(2-fluoro-6-trifluoromethylphenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(2-chloro-5-methylsulfonylphenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(2-chloro-5-dimethylaminosulfonylphenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(2-trifluoromethyl-4-chlorophenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine;

[1-(2-chlorophenyl)-5-methyl-1H-pyrazole-4-carbonyl]guanidine;

[5-methyl-1-(2-trifluoromethylphenyl)-1H-pyrazole-4-carbonyl]guanidine;

[5-ethyl-1-phenyl-1H-pyrazole-4-carbonyl]guanidine;

[5-cyclopropyl-1-(2-trifluoromethylphenyl)-1H-pyrazole-4-carbonyl]guanidine;

[5-cyclopropyl-1-phenyl-1H-pyrazole-4-carbonyl]guanidine;

[5-cyclopropyl-1-(2,6-dichlorophenyl)-1H-pyrazole-4-carbonyl]guanidine; or

a pharmaceutically acceptable salt, hydrate or solvate thereof.

19. A method of reducing tissue damage resulting from ischemia or hypoxia comprising administering to a mammal in need of such treatment

a) an amount of a first compound, said first compound being a compound, a prodrug thereof, or a pharmaceutically acceptable salt, solvate, or hydrate of said compound or said prodrug according to Claim 1; and

b) an amount of a second compound, said second compound being a cardiovascular agent, a glycogen phosphorylase inhibitor, a sorbitol dehydrogenase inhibitor, or an aldose reductase inhibitor;

wherein the amounts of the first and second compounds result in a therapeutic effect.

20. The method of Claim 19 wherein the aldose reductase inhibitor is 1-phthalazineacetic acid, 3,4-dihydro-4-oxo-3-[[5-trifluoromethyl)-2-benzothiazolyl]methyl]- or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

21. The method of Claim 19 wherein the glycogen phosphorylase inhibitor is

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-((3S)-hydroxypyrrolidin-1-yl)-3-oxopropyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl -3-((3S,4S)-dihydroxypyrrolidin-1-yl) -(2R)-hydroxy- 3-oxopropyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [(1S)- ((R)-hydroxy-dimethylcarbamoyl-methyl)-2-phenyl-ethyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [(1S)- ((R)-hydroxy-methoxy-methyl-carbamoyl)-methyl)-2-phenyl-ethyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [(1S)- ((R)-hydroxy-[(2-hydroxy-ethyl)-methyl-carbamoyl]-methyl)-2-phenyl-ethyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(3-hydroxyimino-pyrrolidin-1-yl)-2-oxo-ethyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl -3-((cis)-dihydroxypyrrolidin-1-yl) -(2R)-hydroxy- 3-oxopropyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [2-(1,1-dioxo-thiazolidin-3-yl)-2-oxo-ethyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [(1S)-(4-fluoro-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3RS)-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [2-oxo-2-((1RS)-oxo-thiazolidin-3-yl)-ethyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-amide;

or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

22. The method of Claim 19 wherein the cardiovascular agent is a β-blocker, a potassium channel opener, adenosine, adenosine agonists, a calcium channel blocker, an ACE inhibitor, a nitric oxide donor, a diuretic, a glycoside, a thrombolytic, a platelet inhibitor, aspirin, dipyridamol, potassium chloride, clonidine, prazosin, pyruvate dehydrogenase kinase inhibitors, pyruvate dehydrogenase complex activators, biguanides, NHE-1 inhibitor, angiotensin II receptor antagonists, C5a inhibitors, soluble complement receptor type 1 or analogues, partial fatty acid oxidation inhibitors, acetyl CoA carboxylase activators, malonyl CoA decarboxylase inhibitors, 5'AMP-activated protein kinase inhibitors, adenosine nucleoside inhibitors, anti-apoptotic agents, monophosphoryl lipid A or analogues, nitric oxide synthase activators/inhibitors, protein kinase C activators, protein kinase δ inhibitors, poly (ADP ribose) synthetase inhibitors, metformin, endothelin coverting enzyme inhibitors, endothelin ET A receptor antagonists, TAFI inhibitors, or a Na/Ca exchanger modulators.

23. A pharmaceutical kit comprising:

a) a first compound, said first compound being a compound, a prodrug thereof, or a pharmaceutically acceptable salt, solvate, or hydrate of said compound or said prodrug according to Claim 1, and a pharmaceutically acceptable carrier, vehicle or diluent in a first unit dosage form;

b) a second compound, said second compound being a cardiovascular agent, a glycogen phosphorylase inhibitor, a sorbitol dehydrogenase inhibitor, or an aldose reductase inhibitor and a pharmaceutically acceptable carrier, vehicle or diluent in a second unit dosage form; and

c) a container.